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“THE USES OF THE METHONIUM COMPOUNDS.”

BY

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In the Chair: F. J. M. BENGUÉ, Esq., Hon. F.R.I.P.H.H.

Delivered at the Institute, 15th October, 1952.

Dr. Jules Bernard Bengué, in whose memory these lectures were founded, left the ordinary practice of medicine in Paris to take a degree in Chemistry and thereafter to specialize in the study of anæsthetics. It would surely have pleased him to see how far the synthetic chemist and the pharmacologist are now contributing to his chosen field, not only in local and general anæsthesia and in the creation of analgesics and stimulants, but more recently in the control of respiration and blood-pressure at operation. In expressing my appreciation, therefore, of the honour of being asked to give this lecture, I must at the same time say how appropriate it seems that a pharmacological subject should be discussed. Indeed, I hope to illustrate how chemical and pharmacological studies may assist the progress of anæsthesia, as Dr. Bengué foresaw. It is a pleasure, too, to mention another way in which workers in the physiological or pharmacological laboratory are indebted to Dr. Bengué. His ingenious ethylchloride spray forms a most convenient and simple means of inducing, in animals, a peaceful and rapid anæsthesia; I imagine that almost every laboratory engaged in this sort of work makes use of his invention.

I propose to survey in this talk the uses of a series of chemical compounds called the methonium salts. Recent interest in these compounds began in two independent ways, which I think are worth describing to illustrate some of the factors involved in the origin of a new therapeutic agent. Dr. Ing, at Oxford, who had for long been interested in chemical compounds of this type, particularly in their relationship to curare, turned to investigate how far the high activity of d-tubocurarine, one of the chief curare alkaloids, depended on the distance between its two quaternary nitrogen atoms. With his colleague, R. B. Barlow, he prepared a series of bis-quaternary compounds, of various types, which included the methonium series. My own interest arose in the course of some experiments to see whether changing the terminal grouping of di-basic compounds would alter a certain pharmacological property, that of histamine-liberation (MacIntosh & Paton, 1949). Among the substances tested was the compound which we now call C-8 or octamethonium. Its unexpectedly powerfully paralyzing properties, together with some very intriguing oddities in its action, made it seem that a further investigation would be profitable. Dr. Harold King, then also at the National Institute for Medical Research, to whom a great deal of the fundamental chemistry of the curare alkaloids is due, had been struck, during his war-time work on

compounds with chemo-therapeutic action, by the usefulness of making not just one or two but several members of a series ; and he suggested that such a series might be worth making now. Dr. Zaimis performed these syntheses, and in 1948 and 1949, we examined at the Institute the pharmacological properties of some 13 of these compounds. Barlow and Ing confined their attention chiefly to the neuromuscular blocking action of these drugs and rapidly established the point, which they had set out to test, that the inter-quaternary distance was of great importance in determining the curare-like activity of the molecule, and that the distance which seemed to confer most activity in the series of compounds which they had made, was probably not far from that which nature had achieved in the synthesis of

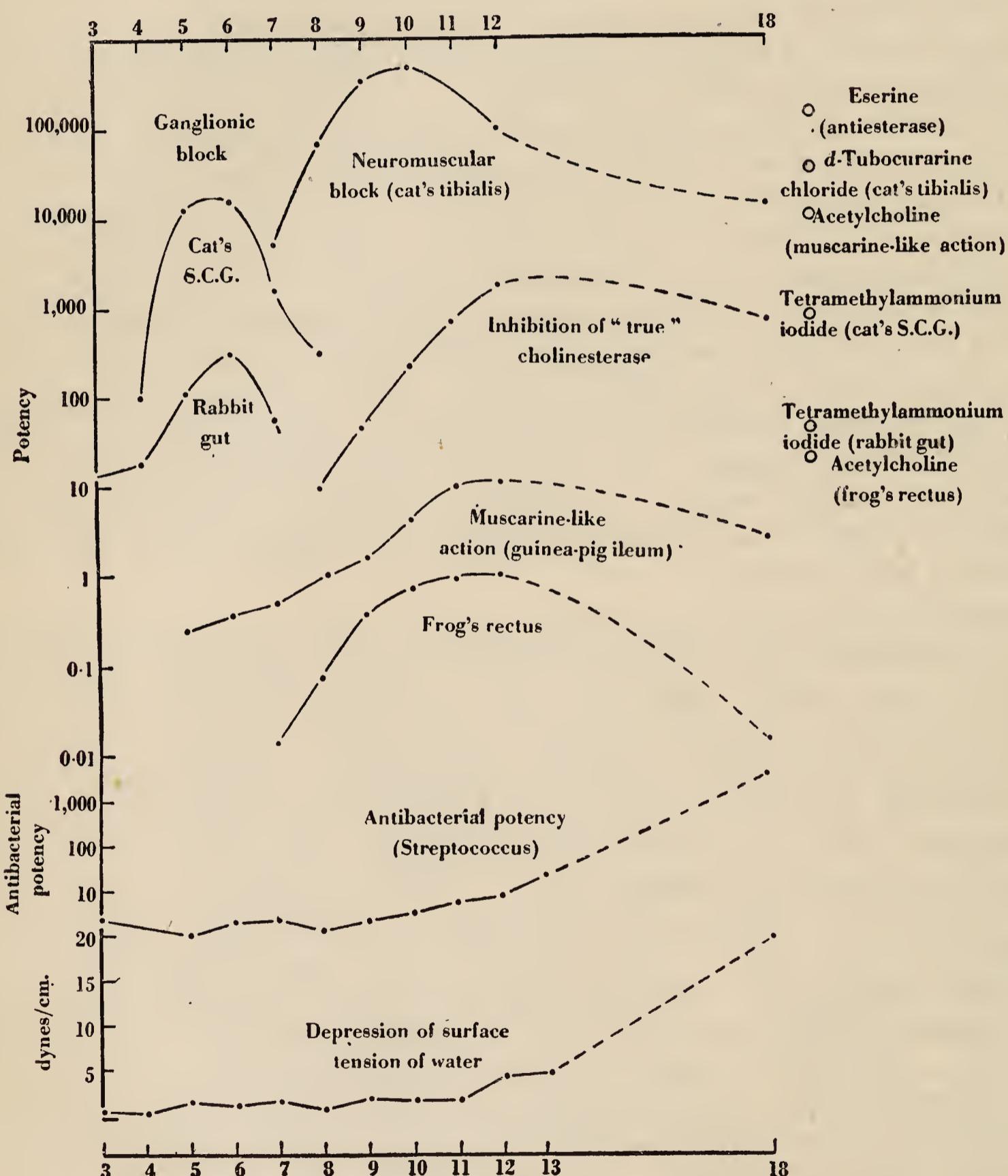


FIG 1.—Summary of the main pharmacological actions of the bistrimethylammonium series. Abscissa : number of carbon atoms in polymethylene chain. Ordinate : logarithmic scale of potency, with arbitrary origins. (From Paton & Zaimis, 1949.)

d-tubocurarine by the bushrope in the South African jungle. As usual nature appeared to have been a very shrewd synthetic chemist ! In this conclusion we entirely agreed with them although we had used other methods and other animals for most of our experiments. We did not make any other series than the single one of the methonium salts, but we pushed our studies of this one series a good deal further, for our tests in whole animals had brought to light so many points of interest that it was obviously important to analyse them in full.

The most important development was that in this series, if the chain is shortened, not only does the neuromuscular paralysing action almost disappear but a new action it revealed—that of ganglionic block. We thus possessed in the methonium series two compounds—the C-10 derivative, or decamethonium, and the C-6 derivative, or hexamethonium, of high activity and considerable specificity of action, which proved to be both of clinical and scientific use.

So much for the laboratory background of these substances. I shall not discuss their pharmacological properties in any more detail save as seems useful to explain certain clinical points, but will turn directly to survey some of their uses in clinical medicine. (For a fuller review of the pharmacological literature, see Paton & Zaimis, 1952.) I am aware that, having been a laboratory worker for most of my medical life, it is dangerous for me to discuss such clinical work. But I have been fortunate enough to be able to talk to many of the clinicians concerned in the different fields and they have generously supplied me with some of the slides which I shall show. With their aid I hope that I shall not go too far astray.

DECAMETHONIUM.

The first of the methonium series to receive any general clinical use was decamethonium. At surgical operation, although the patient may be anæsthetized, his muscles, particularly those of his abdomen, may still be somewhat contracted. This muscular contraction can seriously impede the surgeon. In the old days it was overcome by taking the anæsthesia to a very great depth, when this residual activity of the spinal centres could be finally weakened or abolished. But to do this involves exposing the whole body to a high concentration of the anæsthetic ; and since an anæsthetic is, ultimately, just a kind of tissue poison whose effects are graded and reversible, it is not surprising that from this deep anæsthesia a number of unpleasant after-effects used to follow. The introduction by Griffiths of the use of curare, to produce muscular relaxation and so avoid such depth of anæsthesia, proved extremely successful. But d-tubocurarine, the active principle of the first curare extracts, and later used as the pure substance, has a certain number of disadvantages. It is not very cheap, depending as it does on extraction from natural sources in the South American jungle ; it has some undesirable side-actions, due to its ability to release histamine ; it has some power of paralysing ganglia, which may contribute to the fall in blood pressure sometimes seen with it. Now, decamethonium in animal experiments was to be found highly potent in paralysing the transmission of the nerve impulse to muscle, 10 times more so than d-tubocurarine in the cat, and to be free of the side-effects just

mentioned. Further it was quite easily synthesized and could be made fairly cheaply. Finally, it had, in the cat, a very striking property of weakening the muscles of the limbs without weakening the muscles of respiration. Obviously this would be of great use in human anaesthesia where paralysis of respiration by relaxant substances is usually a disadvantage.

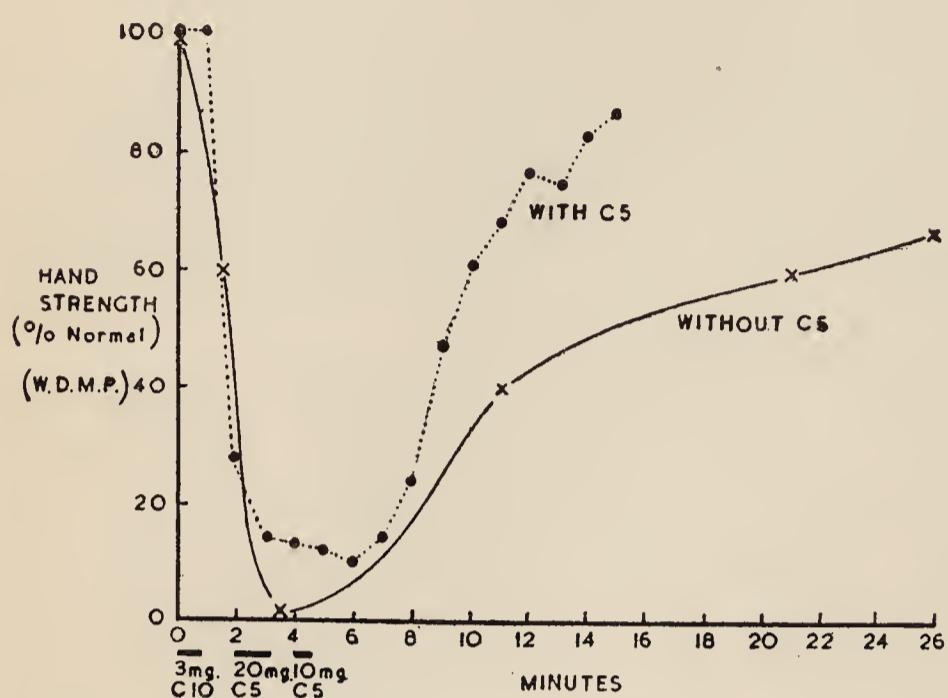


FIG. 2 (a).

Decamethonium was therefore tested clinically and proved to be a satisfactory muscle-relaxant, possessing a shorter duration of action than d-tubocurarine. It has been free of the tendency to cause spasm of the bronchial muscle which had been occasionally observed with d-tubocurarine and has no other harmful effects. It has not been possible, however, to demonstrate in man the same spectacular sparing of respiration as had been found in animals, although in other respects the responses of man and cat muscle are much alike. One defect to its usefulness at present may be the absence of a suitable antagonist. It was found in animal work that an antagonism to the effects of decamethonium could be achieved with penta- or hexamethonium and, indeed, some evidence of this antagonism could be obtained in man. But the doses of hexamethonium or pentamethonium needed were also such as to cause a substantial degree of ganglionic block, and hence a fall in blood pressure. Another antidote has been developed by de Beer and his colleagues in the United States and favourable reports received on its use, but it has not yet been employed in this country. The question of antidotes to such relaxants appears to be an arguable one. Some anaesthetists have found that such drugs as prostigmine, although effective with ordinary doses of curare, do much less good at the time they are really needed when an overdose has been given, and may actually confer a false sense of security if they are administered or even be dangerous in themselves; they maintain that the best antidote is effective artificial

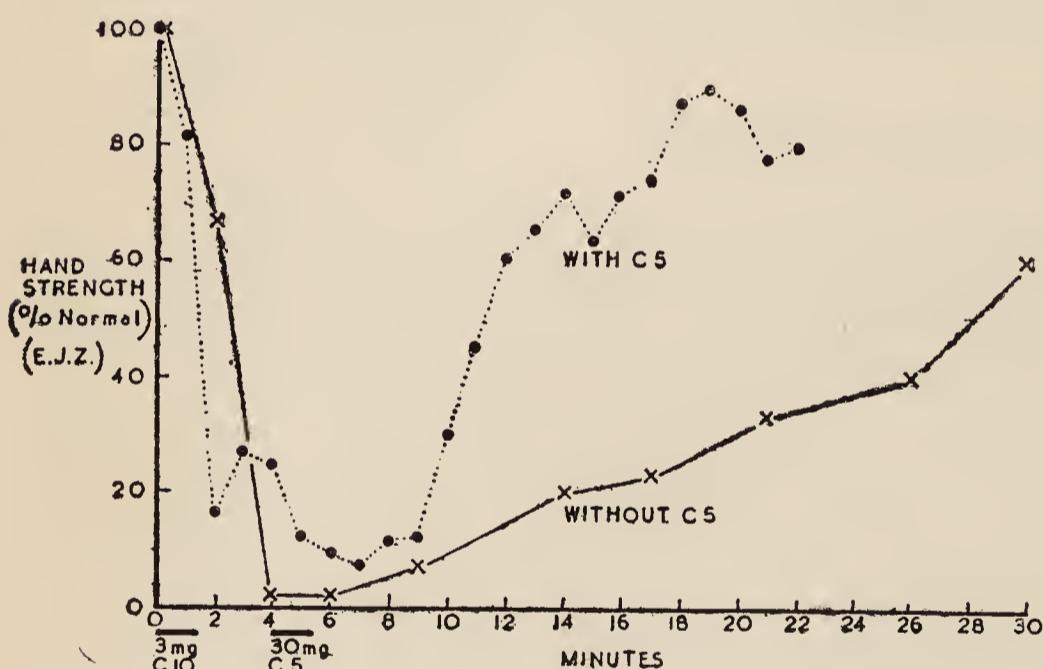


FIG. 2 (b).

Paralysis and return of hand strength.
(From Organe, Paton & Zaimis, 1949.)

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respiration alone. The fact that decamethonium does not possess a very long duration of action further diminishes any need for an antagonist. Others, however, believe it safer to have an antidote available in emergency. Accordingly, decamethonium is probably not so widely used in anaesthesia as it might be were an antagonist readily available.

Another important field in which decamethonium has proved successful is in abating the force of therapeutic convulsions used in the treatment of psychological disease. Although the induction of artificial epilepsy may have a remarkable effect on some depressive states it used to be accompanied by a serious incidence of fractures of the spine. For this reason Bennet and his colleagues introduced the use of curare to weaken the muscular effects of the convulsion without interfering with the electrical discharge from the brain accompanying it. The relative shortness of action of decamethonium and its freedom from producing broncho-spasm made it very successful for this purpose. It was in this field, too, that some vestige of its respiration-sparing action could be detected. Davies and Lewis (1949) compared the reduction of the vital capacity by doses of decamethonium and of d-tubocurarine roughly equally effective in weakening the force of the convulsion; they found that although decamethonium did indeed depress the respiration this depression was significantly less than with d-tubocurarine. As far as I am aware this remains the only quantitative comparison in practice between the reduction of muscular activity desired and the effect on the respiration.

Decamethonium has, like the other relaxants, also been tested in the treatment of tetanus and in the treatment of spastic disease. For the former it proved perfectly satisfactory; to quote from Keir's paper (1950):—"10 p.m., patient restless, crying out, tearful and frightened. After injection, quiet, rational, grateful." Its use in this case supplied a valuable test for its harmlessness on continued administration to man, a total of 135 mg. (about 45 times the single paralysing dose) being administered. In spastic states on the other hand, like other muscle-relaxants, it did not prove possible to relieve the over-contraction of the muscles without simultaneously weakening them for useful voluntary movement.

A particularly interesting development has been the study of the action of decamethonium in the rare disease Myasthenia Gravis. This condition closely resembles poisoning by curare and it is generally believed that there is, causing it, either a circulating curarising compound or some defect in the apparatus of neuromuscular transmission. Now, from the earliest experiments there had appeared to be a curious, and initially most confusing, antagonism between curare and decamethonium which has helped to throw some light on the myasthenic process. On analysis this antagonism proved to spring from the fundamentally different actions of these two drugs. D-tubocurarine, and drugs like it, exert their action by preventing acetylcholine (the natural transmitter released at the ends of the motor nerves), from having its normal action. This is often termed a "competitive action." Decamethonium does not do this but actually imitates the natural transmitter, and itself causes an excitation of the receptor structure on the muscle

fibre. But this excitation instead of lasting, as in normal transmission, for only a few thousandths of a second, persists for minutes or even hours if the dose is big enough. This prolongation of an excitatory process causes an electrical inexcitability of the muscle fibre membrane, so that the excitation set up by acetylcholine release becomes inadequate to excite the rest of the muscle fibre. In short, d-tubocurarine antagonises the natural transmitter, decamethonium exerts transmitter-action in an abnormally prolonged form. This difference in action leads to many differences in detail between the behaviour of the two drugs, and one particular difference occurs in Myasthenia. One would expect that if the Myasthenic is really like a person poisoned with curare, then he should be abnormally sensitive to curare-like substances, but not to a drug like decamethonium. The former has long been known to be the case ; in the last year or two decisive evidence has accumulated that in fact the Myasthenic is relatively resistant to decamethonium. Sometimes this is dramatic : Churchill-Davidson and Richardson (1952) describe a somewhat startling case of a myasthenic girl who received what, in a normal adult, would be equivalent to three times the paralysing dose ; she then helped to push her bed back to the ward. This tolerance is an important fact about Myasthenia and excludes some of the theories of its aetiology. It is also of some practical use in enabling one to give a muscle relaxant to a Myasthenic without the fear of poisoning them because of a special susceptibility to the relaxant.

These applications of decamethonium, in anaesthesia, in electro-convulsion therapy, in tetanus, and in Myasthenia, do not exhaust its usefulness. The fact that so simple a structure should be so active and of such clinical promise in man prompted a good deal of further synthetic chemistry, and many related compounds have been made, of which some have been found clinically useful. Further, the analysis of the action of decamethonium has cleared up some difficulties in our knowledge of neuro-muscular transmission and its response to drugs. One particular point here has been the clarification of the two types of paralysing agent, which one may call curare-like or competitive on the one hand, and depolarizing on the other. A good many comparisons have been made between the "curare-form" actions of various series of compounds, and theories of drug action have been based on these comparisons. But there is little doubt that in some of these series comparisons have been made upon the assumption that all the compounds worked alike, whereas, in fact, some were depolarizing agents and some were truly curare-like. The relaxants most commonly used are probably of the curare-like type, because antidotes are readily available, but it is interesting that decamethonium is no longer alone in the depolarizing group, but has been joined by the closely related succinylcholine. We may expect other members of this group, as the somewhat different technique of handling a depolarizing drug is developed.

Another interesting point lies in the species variation with decamethonium. The cat is very sensitive, the rat extremely resistant, and the mouse and rabbit and monkey in between. When we chose the cat dose as appropriate for the first trials in man, you may guess that we strongly hoped that man did not come outside the range ! In the event it proved that man and cat were almost equivalent.

This is a curious finding ; for it implies that whatever our evolutionary relationship to the monkey, there is no doubt that the cat is a nearer relative so far as muscle pharmacology is concerned.

A final interesting detail may be mentioned. The excitable structures of the body, such as the muscles and the nerves, owe their ability to be excited to the existence of a charge across their cellmembranes. It is as though all these cells of the body were small batteries of strength about a tenth of a volt, in addition to their other properties. Now the action of decamethonium is to discharge this battery over a certain region of the muscle fibre ; so that the patient receiving decamethonium is, so to speak, partially short-circuited all over his body ! It is curious that this should be such an innocuous process and accompanied by no specially notable sensations.

HEXAMETHONIUM.

The first use proposed for the ganglion-blocking methonium salts hexamethonium and pentamethonium was that of an antidote to decamethonium ; as Davison (1951) nicely put it, they "entered the anaesthetist's ken clinging to the skirts of their bigger sister decamethonium." But this was not a particularly appropriate moment of entry, and it was only when she cut her apron-strings entirely that hexamethonium came into her own. This was in the treatment of raised blood pressure or hypertension. Evidence had been accumulating that there was a nervous element in hypertension. It was supposed that activity in the higher centres of the brain (due for instance to worry) caused excitation of the autonomic nervous system and hence rises in blood pressure similar to those produced normally by emotion. If this were the case then obviously a compound which blocked ganglionic transmission should be able to produce a fall in blood pressure in such patients.* This proved to be the case ; indeed, Arnold and Rosenheim (1949) showed that the falls in blood pressure produced with hexamethonium in a series of patients lying supine corresponded quite well with the fall that can be obtained by giving them a sedative. It is important to note that this method of reducing the neurogenic drive leaves the CNS undamaged, and the peripheral effector cells can still be acted on by drugs such as noradrenaline if too great a fall of blood pressure is obtained. All the clinical investigations found that such falls in blood pressure in hypertensives could be obtained ; and that these falls were greatly increased in the upright posture. The effect is sometimes really dramatic, both on the blood pressure measurement and in the patient's symptoms : sometimes almost too much so, so that the question has been raised as to how far in fact lowering the blood pressure was actually desirable in hypertension. (See Figure 3, page 8, overleaf.)

It is worth considering this point a little further. Putting the matter simply, there are two main attitudes to hypertension. The first is that the raised blood pressure is itself the disease and that the pathology of the disease follows from this ; so that any measure which reduces the blood pressure will do the patient good.

* In early clinical studies, both pentamethonium and hexamethonium were used. But it has become clear that the two drugs are almost indistinguishable clinically, save that hexamethonium is slightly more potent. They may be regarded as almost equivalent, but hexamethonium is generally used.

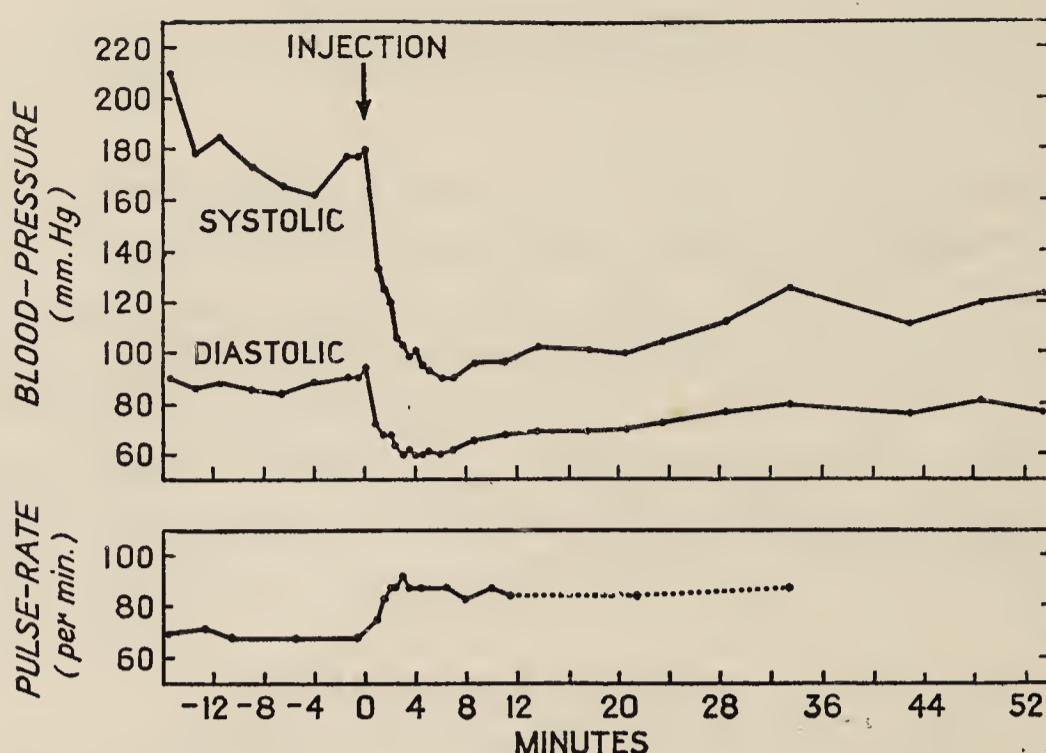


FIG. 3.—Effect of an intravenous injection of 50 mg. of pentamethonium iodide on the blood-pressure and pulse-rate of a woman, aged 57, with benign essential hypertension. (From Arnold & Rosenheim, 1949.)

The second view is that the elevated blood pressure is a sign of another underlying pathological process which is usually placed in the kidneys. The discovery that limitation of blood flow to the kidney will cause a rise of blood pressure in animals focussed attention on the idea that the disease is fundamentally an ischaemia of the kidney and that its proper treatment would consist in raising the blood flow through it. This view of hypertension made it possible to believe that lowering the blood pressure might actually be harmful, in so far as it reduced the blood supply to organs habituated to a raised blood pressure, and in so far as it involved a further reduction in the blood flow through the kidney. A composite view could also be taken in which one might suppose that nervous factors caused a rise in blood pressure ; that this strain on the arterial walls led to arterial damage in various places (including the kidney) ; and that the ischaemia of the kidney led in turn to the appearance of vasoconstrictor substances in the blood which then added their influence to that of the nervous factors already operating. In such a way a sort of vicious circle could be established in which, as the disease develops, humoral factors would play an increasingly important part.

Accordingly, one may put three questions concerning the use of hexamethonium in hypertension :—

- (a) Does lowering the blood pressure with hexamethonium relieve symptoms ?
- (b) Does it relieve the recognizable pathological processes in hypertension, and in particular does it improve renal blood flow or not ?
- (c) Does it exert any other influence on the patient suffering the disease ?

It is quite clear that the first question can be answered in the affirmative. All the clinicians who have used hexamethonium have reported that it usually gets rid of the patients' headaches (which are sometimes dismally severe), often lessens his breathlessness if present, improves or restores his vision, and improves his general sense of well-being. In eclampsia, too, the use of hexamethonium has

sometimes enabled a live birth to take place, by arresting the progress of the toxæmic hypertension.

To the second question, the answer is not yet complete. Some of the pathology of hypertension can certainly be relieved. For instance, an enlarged heart may get smaller as the blood pressure falls. Accompanying this may be the disappearance of abnormalities in the electrocardiogram. If pulmonary oedema has developed, due to failure particularly of the left side of the heart, this may rapidly disperse. In the retina, papillœdema will regress, exudate be absorbed and haemorrhages be cleared.

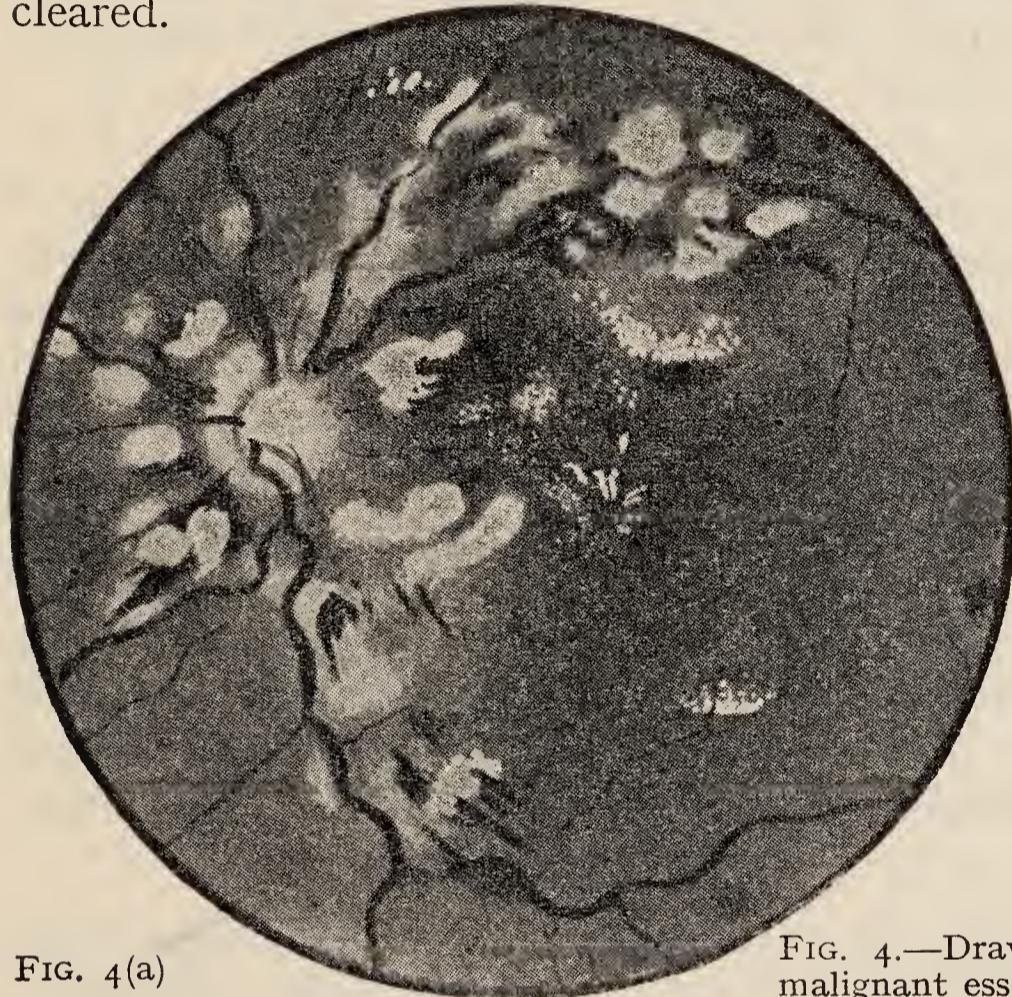


FIG. 4(a)

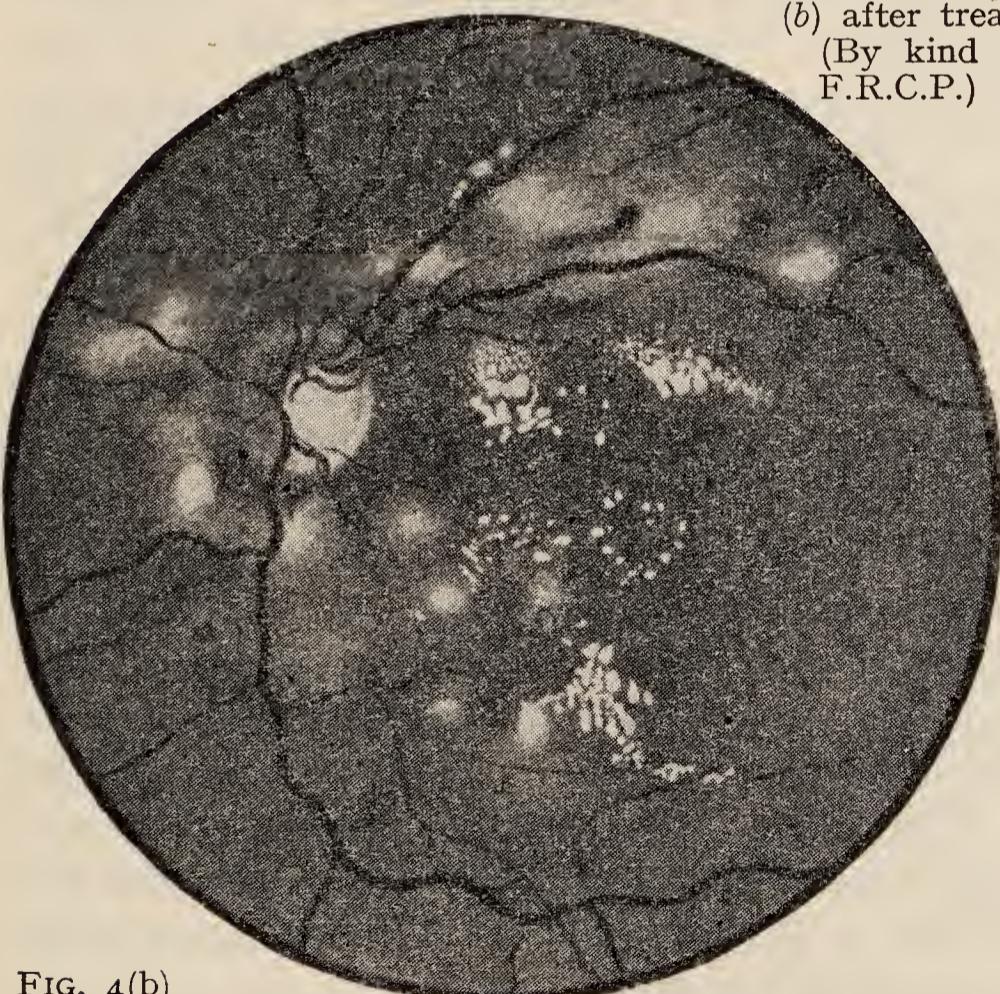


FIG. 4(b)

FIG. 4.—Drawings of the left fundus in patient with malignant essential hypertension: (a) before treatment: (b) after treatment with hexamethonium for 12 weeks.
(By kind permission of Professor M. L. Rosenheim
F.R.C.P.)

But there is no evidence yet that the fundamental processes involved can be reversed. If a patient with hypertension is taken off hexamethonium he almost always relapses to his previous state. If his kidneys have shown signs of damage already, treatment usually does not do much to improve them. It appears, therefore, that though some of the incidental pathology may recover by the lowering of the blood pressure, so far as any renal damage has been done this is more or less irreversible. On the specific question of whether hexamethonium alters renal blood flow, there is still uncertainty, and it is only possible to say that sometimes it is depressed, less often increased, and sometimes unaffected. This is one of the important points that still needs settling.

As to the third question, the main doubts were at first whether the fall of blood pressure might not bring a danger of cerebral thrombosis and of a dangerous reduction of the blood supply to the heart. As already mentioned, so far as the heart was concerned, it appears that the reduction of the load on it does a good deal of benefit, and signs of coronary ischæmia have been few. Similarly, although patients with hypertension are often liable to small transient cerebral episodes, these, in general, do not seem to become more common under treatment, and headaches, in particular, are almost always removed. It seems likely, therefore, that these dangers of fall in blood supply to vital organs are only slight, probably because there is normally some autonomic tone in their vessels, so that the action of hexamethonium in lowering the blood pressure is accompanied by a widening of the vessels to these areas, sufficient to maintain an adequate blood supply.

One particular development needs special mention. It was soon found that patients receiving hexamethonium became tolerant to it and the dose required to produce a given fall in blood pressure steadily rose. It was almost always possible, by increasing the dose, to retain the therapeutic effect. This tolerance passes off when the drug is withdrawn and returns again when treatment is re-started. Little is known about the cause of this, but it probably represents an important clue to the pathological processes underlying hypertension.

From what has been said it is obvious that treatment with hexamethonium is not a simple matter. Its main defects are:—(1) that in most patients the drug must be given subcutaneously several times a day so that the patient has to live a sort of "diabetic" régime; (2) that the dose given to the patient has to be very carefully balanced under supervision in hospital to start with, and (3) that the patient has to get used to having the symptoms of partial ganglionic block of other functions. The advantages of treatment, however, particularly in the severe case, are considerable, sometimes even life-saving. There may be a substantial relief of symptoms and regression of the signs in the eyes and in the heart. The treatment is relatively safe, provided care is taken to adjust the dose carefully and to warn the patient about his sensitivity to posture. There have been very few "toxic effects," and the drug is cheap and easy to dispense.

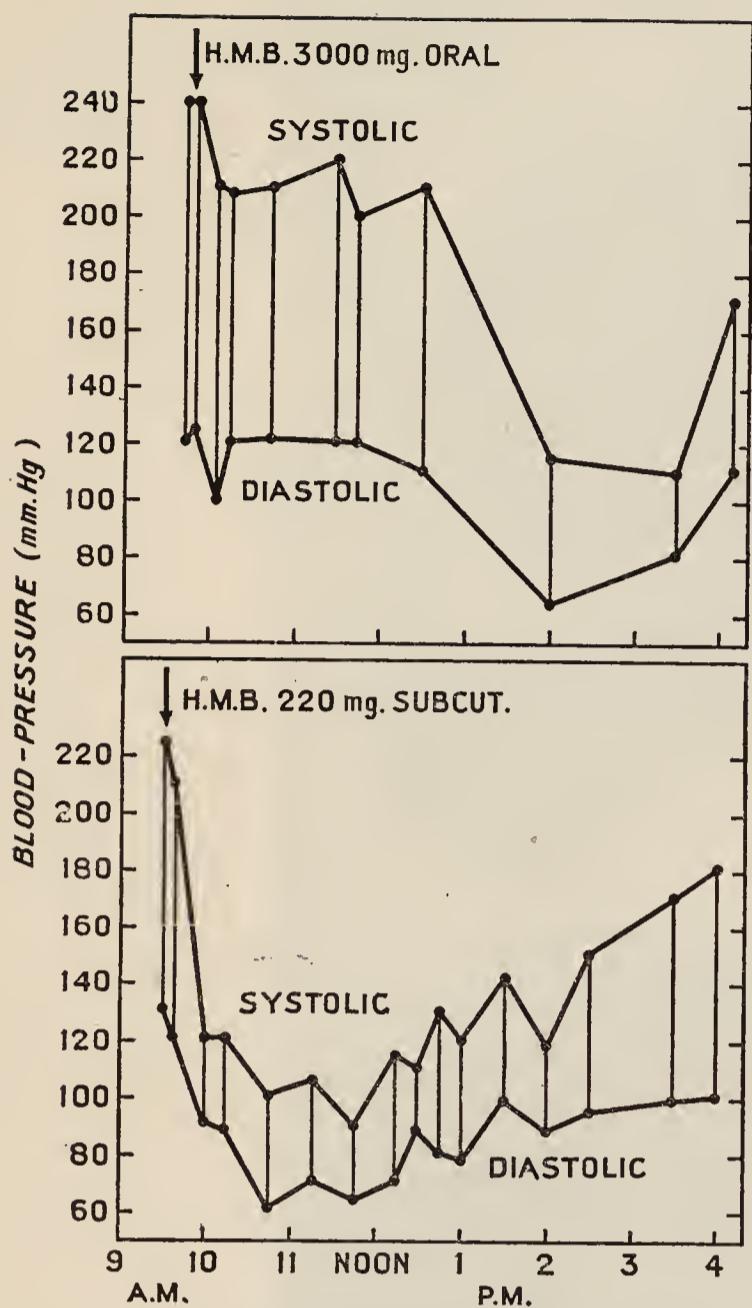


FIG. 5.—Comparison of effects on blood-pressure of sub-cutaneous H.M.B. 220 mg. and of oral H.M.B. 3,000 mg. (case 50). (From Kilpatrick & Smirk, 1952.)

treatment yet available, there are other other treatments, such as the veratrum alkaloids, low sodium diets, thiocyanates, adrenolytics and the like. It appears possible that by the use of these the course of hexamethonium could be temporarily interrupted and tolerance minimized. (4) Finally, in time it might become important to test out hexamethonium in early cases of hypertension in the hope that by early treatment the proportion of cases which advance to renal and other complications may be diminished.

PEPTIC ULCER.

Another disease in which nervous factors have been inculpated is peptic ulcer. Hexamethonium has been shown to depress both the secretion of acid by the stomach (where this is due to nervous influences) and the motility of the stomach and intestine, both in animals and in man. From this has sprung an attempt to test it in therapy of ulcer. So far the final results of such a test have not been published, but it is quite clear that hexamethonium is as effective as large doses of atropine-like substances, in reducing secretion of acid in ulcer patients and it has also been shown to depress the exaggerated motility of the stomach in such patients.

For the future there is no doubt that other drugs will be developed in an attempt to remove the disadvantages of hexamethonium. Progress along three lines may be expected:—(1) Hexamethonium usually needs to be given parenterally because it is poorly and irregularly absorbed by mouth. (Fig. 5). Considerable importance attaches to being able to prolong its action, in order to minimize the number of injections a day. Recently it has been shown to be possible to prolong the action considerably by mixing the drug with a viscous medium made of dextran or polyvinylpyrrolidone. (2) In the early pharmacological work evidence was obtained that different ganglion blocking agents might affect different ganglia to varying degrees. One may expect that in time substances may be found which influence the ganglia controlling the blood pressure more than those affecting the eye or the viscera. (3) Another development in progress is the combination of hexamethonium with other treatments, which may be particularly important in avoiding the development of tolerance. Although in general the therapy of hexamethonium is the most effective medical



FIG. 6 (a).—Control : half-hour film, showing greater part of meal in small intestine. (From Douthwaite & Thorne, 1951.)

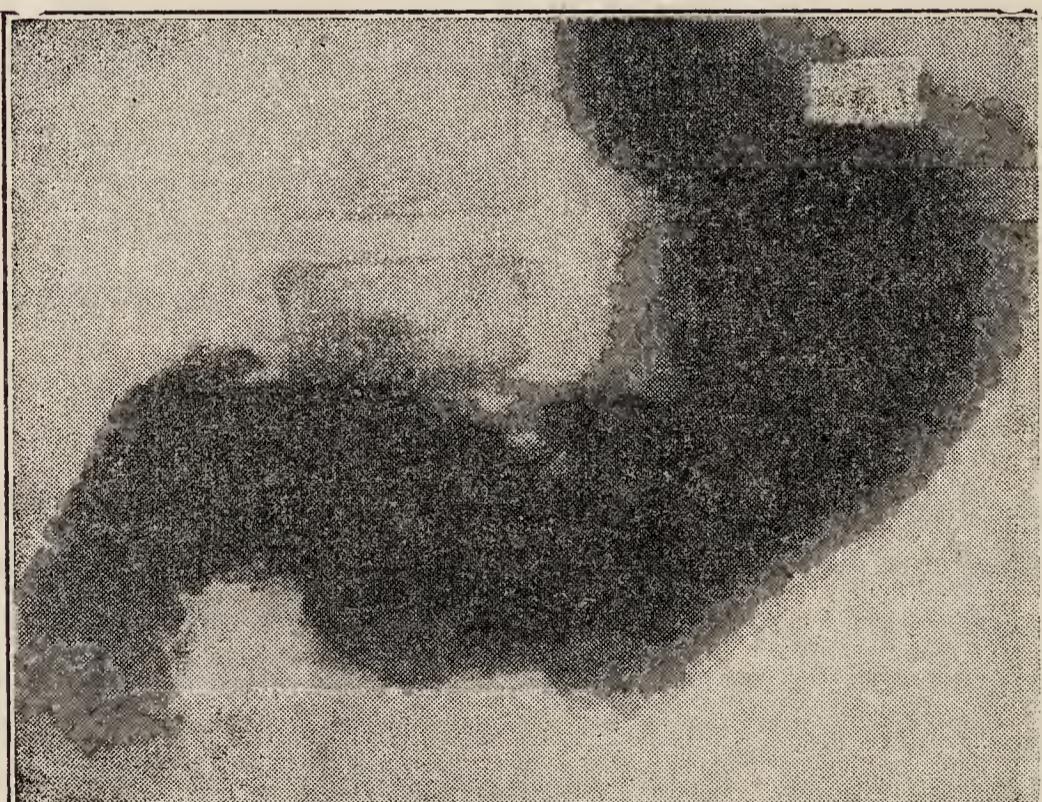


FIG. 6 (b).—100 mg. of C6 : half-hour film. Note the retention of barium in stomach and duodenum. (From Douthwaite & Thorne, 1951.)

The early clinical findings in a group of severe ulcer patients appeared promising, but the assessment of therapy in this disease is one of the most difficult in medicine, and much more work remains to be done.

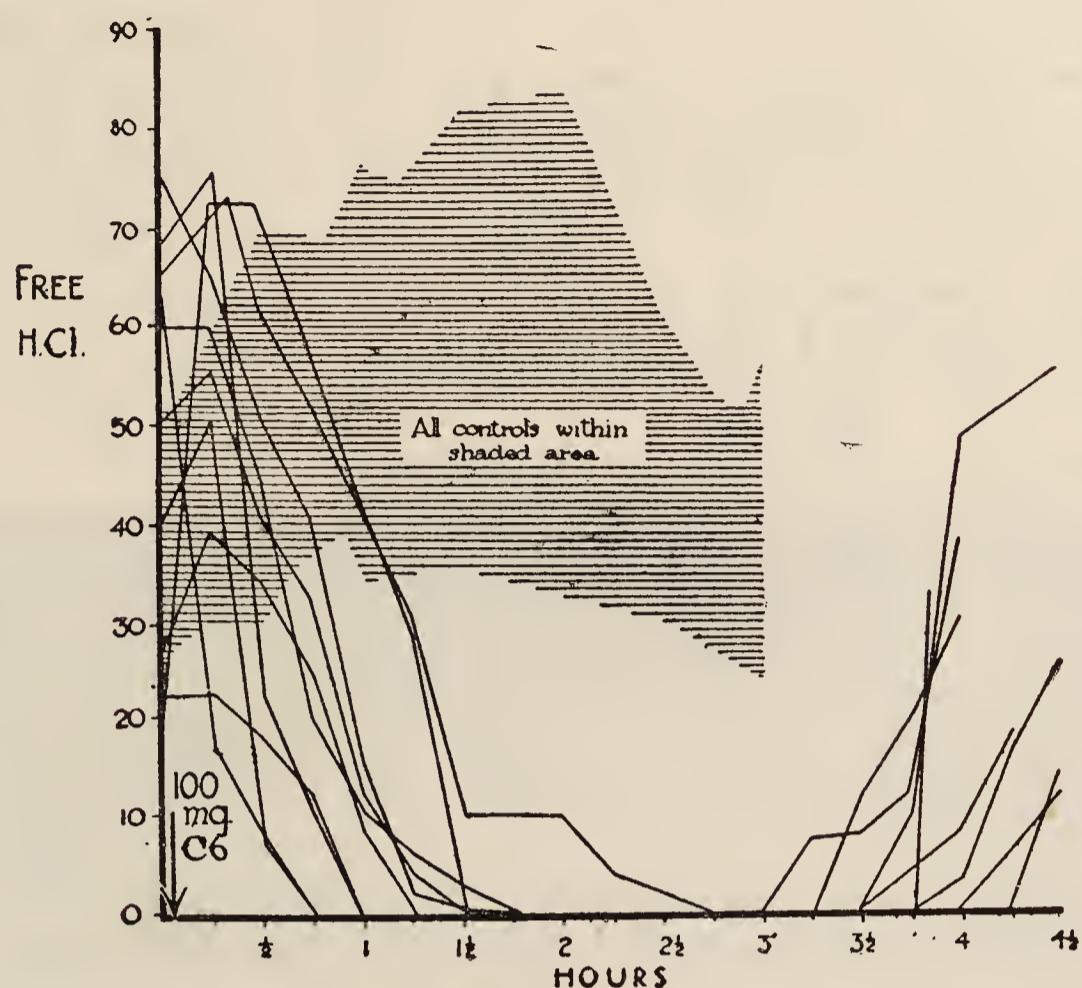


FIG. 7.—Gastric acidity: control readings and after C6.
(From Kay & Smith, 1950.)

REDUCTION OF BLEEDING IN SURGICAL OPERATION.

The third important use of hexamethonium is to reduce bleeding at surgical operation. It had been shown some years previously that this end could be achieved in two ways, either by a deliberate haemorrhage of one to two pints of blood before the operation began, or by inducing a spinal anaesthetic. The former of these simply lessens the blood volume directly, lowers the blood pressure and produces a reflex constriction of blood vessels in an attempt by the body to keep the blood pressure within tolerable limits. Spinal anaesthesia works by interrupting the outflow of autonomic activity at the level of the spinal cord, so depriving the blood vessels of their normal tone and allowing the vessels to dilate and blood to pool in the veins when the patient is tilted. Both these procedures are relatively complicated. We owe chiefly to Enderby the establishing of a method for using hexamethonium for the same purpose. Its use simplifies technique considerably, replacing spinal anaesthesia by a simple intravenous injection of a drug of transient action, whose effects can be readily antagonized.

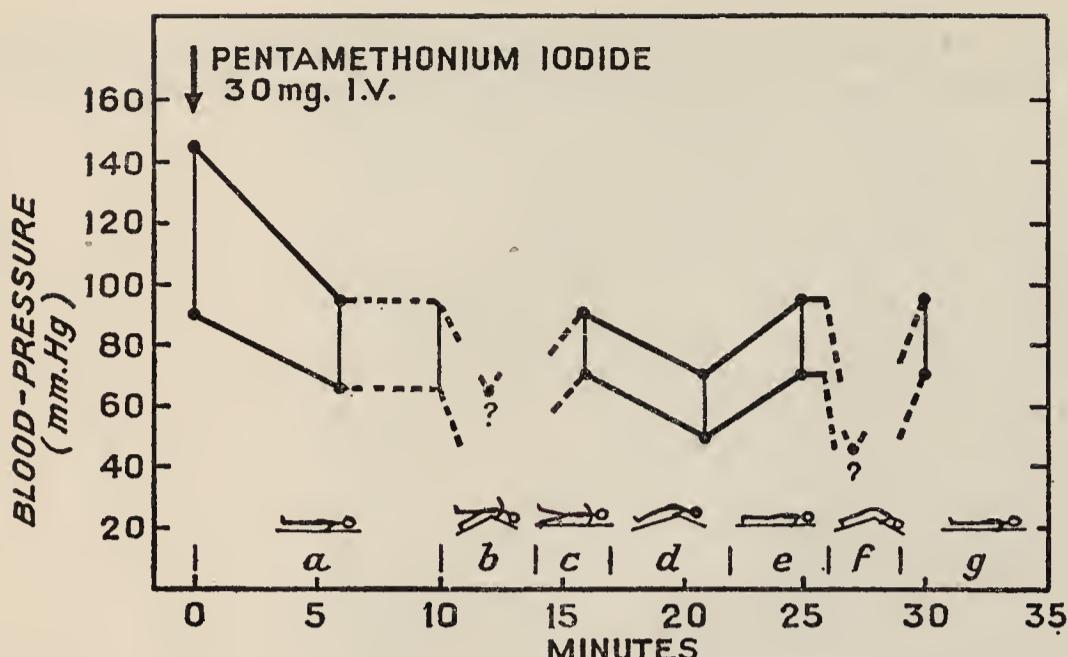


FIG. 8.—Effect of posture on blood pressure of anæsthetized healthy male, age 40, after pentamethonium iodide, showing importance of gravitational pooling of blood in legs in production of hypotension. Blood-pressure before operation was 125/75 mm. Hg. A minor operation on the foot was completed in 30 minutes. Blood pressure at end of operation and at start of investigation was 145/90 mm. Hg. Postures : *a* and *g*, supine horizontal : *b*, right lateral jack-knife ; *c*, right lateral horizontal ; *d*, supine hyperextended ; *e*, prone horizontal ; *f*, prone jack-knife. (From Enderby, 1950.)

fall in blood pressure can be brought about in many patients. A third factor is the raising of the operation field above heart level. This probably accounts for the fact that plastic operations on the head and neck, (Fig. 9), neuro-surgery and operations on the ear, nose and throat, have all proved to be extremely successful occasions for this technique. The effect is, indeed, sometimes really dramatic.

It is uncertain as to how the reduction of haemorrhage is achieved. In order to lessen bleeding, one may imagine that two things are desirable. First that the pressure in the vessels which will be cut at operation should be as low as possible at the point where they are cut ; second that the rate of flow of blood from the cut stump should be as sluggish as possible, so that clot, as it forms, does not tend to be washed away. The initial injection of hexamethonium reduces the hydrostatic pressure in the larger vessels, although it may also actually increase the blood pressure in the capillaries in some regions. If the patient is now tilted from the supine position the reflexes which normally operate to maintain an adequate blood pressure to the uppermost parts have been paralysed and blood can pool in the dependent parts. In effect then, posture is a means of lessening the effective circulating blood volume and consequently produces a further fall in blood pressure. One must suppose that as a rule the body now possesses relatively dilated arterioles containing blood at low pressure, and dilated veins in the dependent parts ; and we can further reduce the blood pressure at the site of operation by raising it above heart level. Thus we have three factors, all of which will contribute to lowering the pressure in the arterioles of the operation area : the release of vasoconstrictor tone causing a general fall in blood pressure, the use of posture to pool blood in the dependent parts, so as to lower the blood pressure still further, and the raising of the operation site above the rest of the body.

Enderby has found that there are several factors involved in the successful use of this technique, and it is worth describing these before considering how the reduction in haemorrhage is brought about. To secure a good effect it appears to be necessary to reduce the systolic blood pressure to about 60-70 millimetres of mercury. It is only rarely that it is possible to do this, simply by injecting hexamethonium. In most cases some postural adjustment is needed. With a sufficient dose of hexamethonium and suitable tilting the required

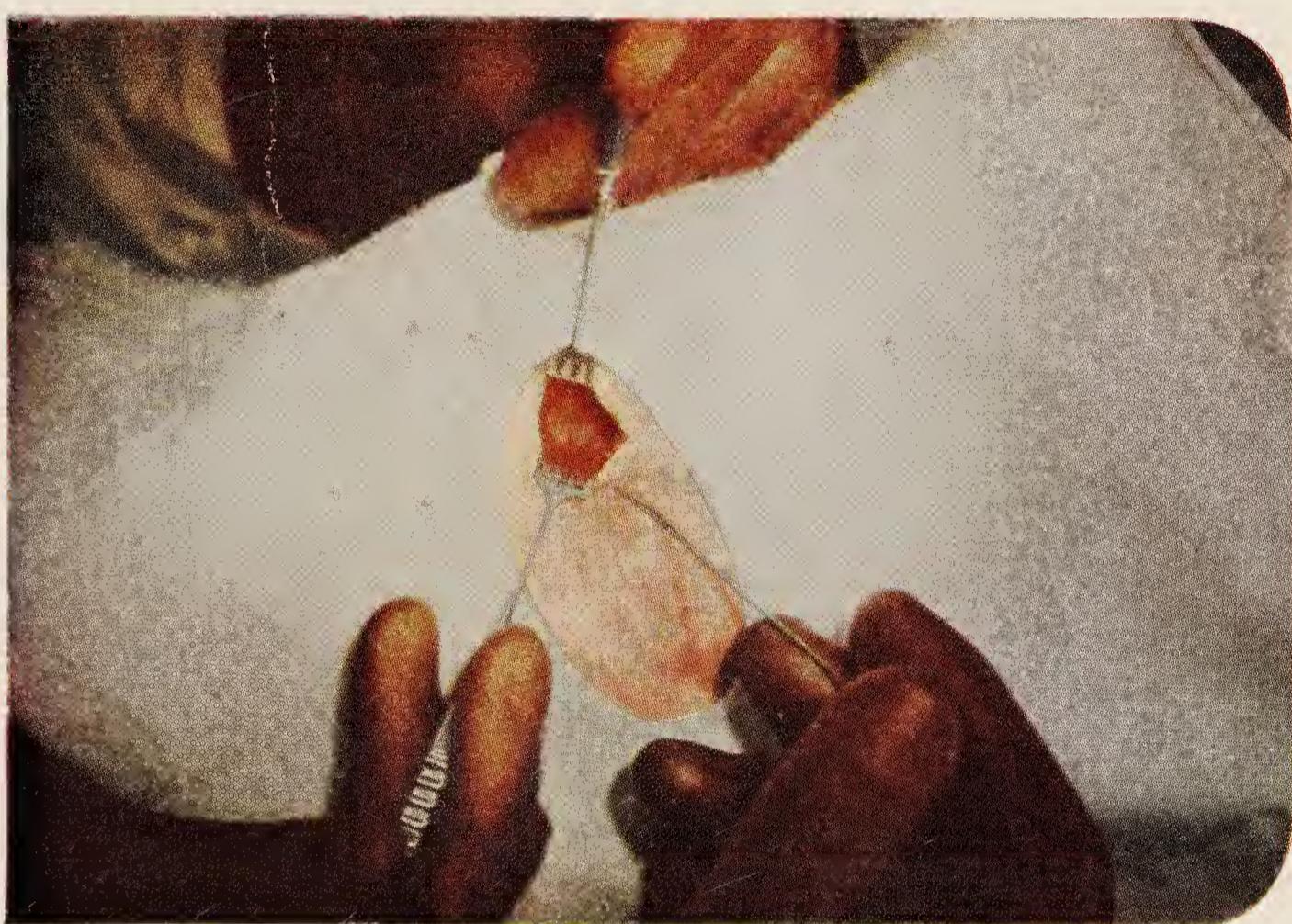


FIG. 9.—Photograph of operation for a blocked tear duct (right eye).
(From the film "Reduction of Surgical Haemorrhage by Controlled Hypotension,"
by courtesy of May & Baker Ltd.)

All this will mean that if arteries or arterioles are transected blood will flow from them less rapidly, and a clot will need to be less firm in order to hold against the blood pressure. But, in addition, when one looks at the skin during the use of this technique it is so blanched and the operation is so much like the dissection of a corpse that one must suppose that the blood *flow* to the skin has been enormously reduced as well (Fig. 9). It is difficult to be certain of this because the bloodlessness of the field might be simply due to the low blood pressure ; the pallor of the skin does not prove a deficient circulation, for skin colour is a poor index of this ; and the fact that the vessels are relaxed means that smaller pressures than usual are required to maintain an adequate flow. It is probably fair to suppose, in short, that the reduction of intravascular pressures contributes considerably to the reduction of bleeding and that sometimes, at least, the reduction of flow through the vessels at the operation site also permits more rapid clot formation.

One of the most striking features of this technique has been the evidence obtained that a patient may not only survive the reduction of his blood pressure to such low levels but that he is then suitable for more or less prolonged surgical operation. The falls in blood pressure produced are such as, a few years ago, would have been regarded as representing profound circulatory "shock" and would have led to the institution of vigorous therapy. Recent evidence has accumulated to show that prolonged hypotension due, for instance, to haemorrhage or trauma, may enter an irreversible stage from which no transfusion or other treatment can bring recovery. How is it, therefore, that patients may safely survive this new technique ? There are probably two important factors. The first is that there is no reactionary peripheral vasoconstriction. This means that the capillary pressures approach much nearer to the pressures in the arterioles than, for instance, after haemorrhage. It is indeed surprising to observe in patients with these low blood pressures how pink and warm the skin is on the body at heart level or below. Despite these low blood pressures, therefore, the peripheral dilation still seems to permit a sufficient flow of blood to the tissues. The second factor is probably that there has been no attack on the permeability of the capillaries. After trauma or in the shock produced by histamine, capillary permeability is usually seriously damaged. With haemorrhage, too, there is evidence that vaso-active materials are released. As soon as such a defect of permeability has been maintained for any length of time it becomes difficult to restore the *status quo* by any means. But after ganglionic block there is no reason to suppose that any permeability changes occur, and clinical experience has shown that all the vascular changes are rapidly reversible by returning the patient to the horizontal or head-down position, and by sympathomimetic drugs.

This is not to say, however, that the evidence is complete, that reduction of blood pressure to these low levels is perfectly safe. It is difficult in man to measure blood flow in the vital organs accurately. But it has been shown that the blood flow to the kidneys may be hardly affected ; electrocardiograms taken during this technique have failed to show any sign of coronary ischaemia ; so far as the brain is concerned normal electroencephalograms have been taken throughout an

operation using this technique, and, indeed, the collaboration of the patient has been obtained, even though his blood pressure was at these low levels. Some evidence has been brought that severe hypotension may damage the liver, but this damage does not begin to appear until the pressure is lowered below 60 millimetres of mercury.

It is probable that the danger of the method lies in another direction. During ganglionic block, as has been described above, the patient is very sensitive to postural adjustments. During the operation this is constantly under the eye of the anæsthetist. But the effects of hexamethonium have usually not entirely worn off by the end of the operation and cases have occurred in which on a trolley or in the ward patients have been kept unconscious, with legs tilted downwards, sufficiently to lower their blood pressure to dangerous levels, without this fact being known. The use of this technique and the way it makes the patient so vulnerable to tilt mean that special nursing technique is necessary. Similarly the patient is very vulnerable to haemorrhage and if haemorrhage does take place under these conditions, the fall in blood pressure produced is much greater than normal. Consequently blood lost at operation, if by chance the loss is significant, must be carefully replaced.

The use of this technique is still in the experimental stage, but it seems to be recapitulating the story of the control of respiration by curare. At first the latter was regarded as highly dangerous ; then came an exploratory period when it was used in operations for which it was not really suited ; finally it has settled down to become a standard technique of which the details have been fairly well worked out. The use of "controlled circulation" is, perhaps, passing the stage in which most people's reaction was a feeling that it must be very dangerous and entering the phase in which, because of the delightfully clear operative fields it may present to the surgeon, it may be used unjustifiably. Nevertheless, the assistance it gives, particularly in neuro-surgery and in plastic surgery, may well make it one of the most important developments in anæsthetic technique and one which reflects great credit on the courage of its pioneers.

OTHER USES.

Hexamethonium has also proved valuable in other conditions. In spastic and various types of peripheral vascular disease (such as arteriosclerosis, venous thrombosis, embolism and causalgia), it is possible in some cases to improve the blood flow considerably by paralysing the sympathetic ganglia supplying the part concerned. Similarly, in conditions where sweating of the hands is excessive, ganglionic block may be effective. As a rule surgical methods are preferable, because the interruption of autonomic function can be localized to the limb concerned. But where operation is not desired, treatment with hexamethonium is simple.



FIG. 10.—(a) Quinizarin sweating test on a patient with hyperhidrosis before injection of C5.



(b) The same test as in (a) but after injection of C5 (From Burt & Graham, 1950.)

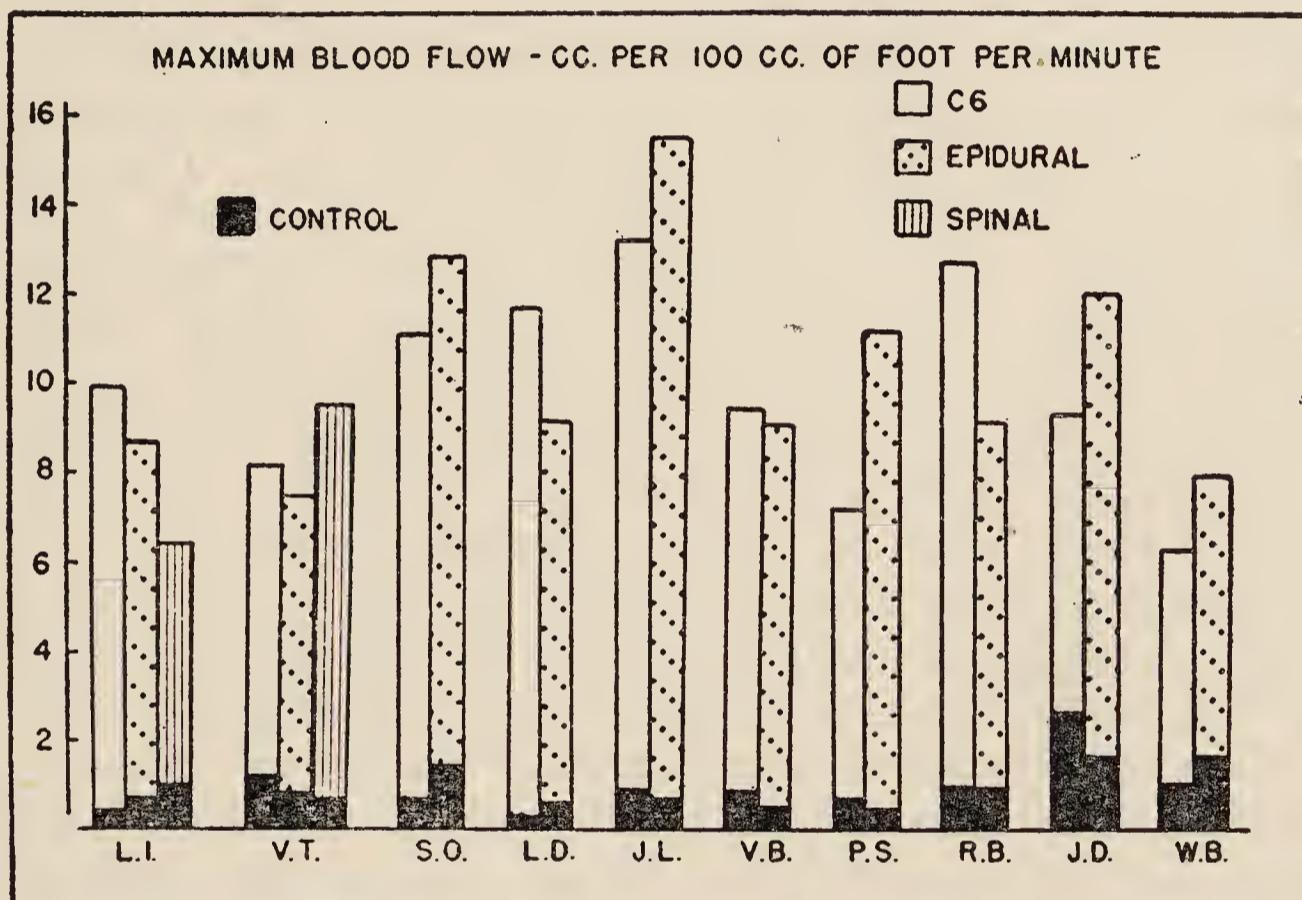


FIG. 11.—Chart of the maximum blood flows in the left foot following hexamethonium as compared to lumbar intrathecal or epidural block in ten normal subjects. (From Schnaper *et al.*, 1951.)

Hexamethonium has also been of use in depressing over-activity of a small intestine such as occurs in some forms of colitis or after gastrectomy. It seems to be dangerous to use too large doses; the depression of mobility of the intestine leads to an accumulation of the contents in the intestine and hence to distension of the gut. If the intestinal wall is diseased, this distension may place too great a strain on it and cause a perforation. But little work has been done in this field and the conditions of safe usage remain to be found.

A use of quite a different kind, and of a more general nature is in physiological analysis of autonomic activity and of drugs which influence it. Hexamethonium has proved to be highly specific in its action, so that the reduction of a function in

its presence is strong evidence that autonomic activity has been involved. In this way it is possible that the somewhat disreputable concepts of "vagotonia" and the like might be given some quantitative meaning. This awaits an investigation on a quantitative scale of the action of hexamethonium in normal individuals.

Finally, I would like to turn to some general considerations. Many of the methonium salts have been known for years. Hexamethonium and decamethonium were first synthesized as long ago as 1910-11 and have sat on the shelf with their therapeutic possibilities unrecognized over 35 years. This raises immediately the question, what are the conditions necessary for taking such drugs off the shelf and in to clinical use?

Many elements can be recognized in the ontogeny of therapeutic agents. The starting point is usually a more or less chance observation in an academic laboratory. The *first* requirement therefore is an environment in which such chance observation may be made and in which there is time to investigate it not so much for possible therapeutic importance, as simply to find a satisfactory explanation for it. *Second*, there is necessary a scientific climate such that those observations which hold promise may be recognized for what they are. In the case of the methonium salts, this climate was provided by the recent recognition that the effects of nervous excitation were transmitted to muscle cells and to ganglion cells by a chemical mediator, acetylcholine. In addition, interest had been revived in curare by the work of King, Griffiths and Bovet, and in autonomic ganglia by the work of Acheson and Moe and their colleagues in studying tetræthylammonium. Although the latter substance is severely limited so far as practical use is concerned, this work did a great deal to stimulate interest in the potentialities of other ganglion blocking agents. *Third*, when the pharmacological work has been done it is necessary to make the awkward transition from animals to man. The growth in recent years of human experimentation has made this transition significantly easier and the fact that the fundamental pharmacology was done in the laboratories of the Medical Research Council at the National Institute for Medical Research eased the transition still further by the link existing through the M.R.C. with clinical units all over the country. But it must be added that a *fourth* factor has played an important part, that of what may be termed "private enterprise." A great deal of progress could be made by more or less arranged trials; but many important steps in the development of the usefulness of the methonium salts were completely spontaneous. Such were its first trial in the therapy of peptic ulcer at Glasgow, in which it was incidentally shown that the drug could be given orally with success. Another was the success of Campbell and Robertson in this country, and of Smirk and his colleagues in New Zealand in showing that despite difficulties of control, treatment of severe cases of hypertension with hexamethonium could be really valuable. A third example was the use of hexamethonium to reduce hæmorrhage at operations, from which has sprung what may be one of its most important uses.

It is obvious, therefore, that for the recognition and exploitation of a somewhat novel mode of therapy a great many conditions have to be met. Probably

neither the original observations, nor the final clinical application can be successfully "planned"; and yet in the intermediate stages, deliberate investigation may be of great value. It is obvious that all types of work find their place in advances of this type.

Lastly I would like to return, as I started, to a pharmacological reference. Those whose task it is to look at a little of the history of therapeutics rapidly develop a certain cynicism about therapeutic agents. One can estimate the interest taken in the methonium compounds by counting the number of papers written each year on them, and Fig 12 (a) shows in this way the relatively rapid exploitation of these drugs. But one may match such a graph with another one (Fig. 12 (b)), compiled by D'Arcy Hart from papers concerning the use of gold for the treatment of tuberculosis. It shows how a tremendous volume of work petered out, until now gold is almost of archaeological rather than clinical interest. Are there any reasons to believe that a similar fate will not befall hexamethonium and ganglion blocking agents like it? There are, I think, at least three points which allow one

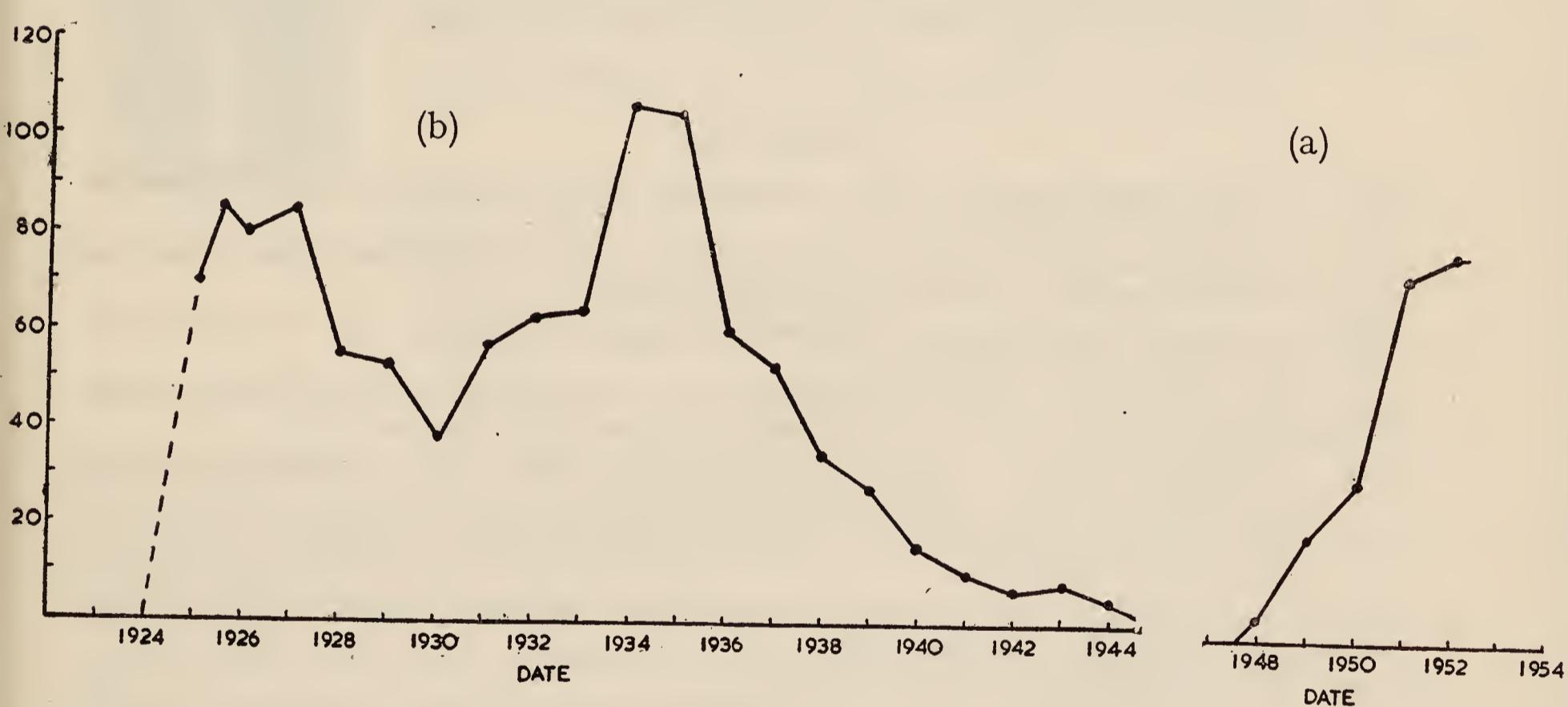


FIG. 12 (a).—Number of papers each year about one or more members of the methonium compounds.

FIG. 12 (b).—Number of papers each year about the use of gold in tuberculosis. (From D'Arcy Hart, 1945.)

to be somewhat more optimistic. In the first place we know fairly precisely what action it is that hexamethonium produces in the body, but this was never known about the effects of gold in tuberculosis; all that could be said was that perhaps it had a bactericidal action, or stimulated the reticulo-endothelial system, or excited a focal reaction. Second, rigorous testing of the benefits of gold in tuberculosis was never carried out, and it is probably only recently that the methods have become recognized by which such tests could be conducted. With hexamethonium, on the other hand, most of its effects are obvious and relatively easy to measure.

Some, such as the effect on blood pressure, the dry field at operation, and the tolerance of the myasthenic are really dramatic. Finally, the actions of gold on the human organism are multiple and complicated ; so that even without knowing the fundamental basis for them it would still be hard to know which of the various aspects of the action of gold was the one that mattered. Hexamethonium, on the other hand, is a specific drug and whatever may be the final answer about its usefulness in therapeutics there will be obtained in time a clear "Yes" or "No," not only to whether hexamethonium is of use in particular circumstances, but also to whether the whole principle of the interruption of autonomic activity in therapeutics is a valuable one. Experience with hexamethonium illustrates, in short, that it is never a waste of time to study in man the effects of a specific drug whose properties are properly analysed and understood ; and I believe that it is in the development and use of such drugs that pharmacology is going to make its greatest contribution to anaesthesia and therapeutics.

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